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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/675,172 | DONOVAN, STEPHEN | |
| | Examiner | Art Unit | |
| | VANESSA L. FORD | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 May 2008 and 15 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22-28,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28 and 36-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed May 15, 2008 has been entered. Claims 1-21 and 29-35 have been canceled. Claim 22 has been amended. Claims 22-28 and 36-37 are under examination.

### *Rejections Withdrawn*

2. In view of Applicant's amendment and response the following rejections are withdrawn:

(a) rejection of claims 22-28 and 36-37 under 35 U.S.C. 112 second paragraph, page 3, paragraph 3.

(b) rejection of claims 22, 28 and 36 under 35 U.S.C. 103(a), pages 3-6, paragraph 4.

(c) rejection of claims 23-24 under 35 U.S.C. 103(a), pages 6-8, paragraph 5.

(d) rejection of claims 25 and 27 under 35 U.S.C. 103(a), pages 8-10, paragraph 6.

(e) rejection of claims 26-27under 35 U.S.C. 103(a), pages 10-12, paragraph 7.

## *New Grounds of Rejection*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 22-24, 28 and 36 are rejected under 35 U.S.C. 103(a) as unpatentable over Pearce et al *(U.S. Patent No.6,087,327 issued July 11, 2000)* in view of Mohr et al (*U.S. Patent No. 5,591,767 issued January 7, 1997)* and further in view of Singer et al *(Acad Emerg Med, Nov. 1998; 5(11), p. 1051-6) (Abstract only).*

Independent claim 22 is drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of: (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum and (b) applying a fluid to the patient's skin, (c) applying a transdermal patch to the skin of a patient in an area that had the stratum corneum disrupted in step (a), the transdermal patch comprising; i) a pharmaceutical composition comprising a stabilized botulinum toxin provided in a dried state and an enhancing agent that is mixable with the stabilized botulinum toxin provided in a dried state and facilitates transdermal administration of a botulinum toxin in a bioactive form to a subdermal target site of a human patient without being administered to the patient's

circulatory system; and ii) an adhesive layer disposed to one side of the transdermal patch to removably secure the patch on the patient's skin; when the pharmaceutical composition is incorporated into the adhesive layer; and (d) solubilizing the botulinum toxin provided in the dry state with the fluid, wherein solubilization of the botulinum toxin permits diffusion of the botulinum toxin from the adhesive layer into the patient's skin thereby reducing neurotransmitter release in a subdermal structure.

Pearce et al teach that botulinum toxin inhibits or impairs neurotransmitters (column 1). Pearce et al teach that it is contemplated that the neurotoxin would diffuse to the neuromuscular junctions resulting in inhibition of acetylcholine (Ach) release, for example and at sufficiently high dosages complete paralysis of the muscle will occur (column 9). Thus, Pearce et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient. Pearce et al teach that the admixtures used in the invention include botulinum toxins A-G (see the Abstract)(claim 28). Pearce et al teach that the transdermal delivery of botulinum toxin comprising a depot (botulinum toxin in the dried state) administration of botulinum toxin into a selected area (column 9). Pearce et al teach that gelatin to be used in pharmaceutical compositions (column 9). Pearce et al teach that the botulinum toxin compositions are dried (columns 8-9). Pearce et al teach that the depots of the invention can be used in transdermal diffusion (column 9).

Pearce et al do not teach a transdermal patch.

Mohr et al teach transdermal patches that are adhesive patches where the drug and the enhancer (enhancing agent) are formulated into the skin adhesive layer

(column 7) (claim 36). Mohr et al teach that the adhesive layer serves both as the enhancer reservoir as well as the adhesive layer which attaches the patch to the patient's skin (column 7). Mohr et al teach that the trandermal patches comprises an impermeable backing layer which is sealed at its periphery to a rate-controlling membrane layer thus defining a drug depot (column 8). Mohr et al teach that the drug depot generally contains the drug and optionally an enhancer and/or gelling components (column 8). Mohr et al teach that an adhesive layer on the rate controlling membrane attaches the patch to the patient's skin (column 8).

Pearce et al nor Mohr et al teach the claim limitation of "non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum" or "wherein the stratum corenum is disrupted by abrasively removing the stratum corenum" or "wherein the stratum corenum is disrupted by applying an adhesive material to the patient's skin and removing the adhesive material applied thereto".

Singer et al teach that tape stripping is an effective in disrupting the stratum corenum barrier (See the Abstract)(claim 23 and 24). Singer et al teach that removal of the cornified layer of skin resulted in a more rapid anesthetic effect of the drug (EMLA cream) (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to modify the method of reducing neurotransmitter release in a subdermal structure of a patient as taught by Pearce et al to include the transdermal patch of Mohr et al which incorporates drugs and skin enhancers (e.g. botulinum toxin and the enhancing agent)

into the adhesive layer and non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum corenum as taught by Singer et al because Mohr et al has demonstrated that this design of transdermal patch is simple but effective in delivering drugs to the skin and Singer et al teach that tape stripping enhances absorption of drugs into the skin. It would be expected, absent evidence to the contrary, that a transdermal patch comprising botulinum toxin and an enhancing agent within the adhesive layer would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of a patient's skin that has been non-chemically disrupted by tape stripping. Thus, the combination of references teach the claimed method of reducing neurotransmitter release in a subdermal structure of a patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art that botulinum toxin inhibits or impairs neurotransmitters. See Pearce et al. Transdermal patches that incorporate drugs and skin enhancers into the adhesive layer are known in the art. See Mohr et al. Tape stripping is a non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum corenum. See

Singer et al. Thus, it would be obvious to reduce neurotransmitter release in a subdermal structure of a patient by using a transdermal patch that incorporates the drug or enhancing agent or into the adhesive layer and non-chemically disrupting the skin of the patient by tape stripping prior to applying the transdermal patch because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results. The combination of references teach the claimed invention absent convincing evidence to the contrary.

4. Claims 25 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearce et al, Mohr et al, Singer et al as applied to claims 22-24, 28 and 36 above, and further in view of Mitragotri et al *(Science, Vol. 269, August 11, 1995).*

Dependent claims 25 and 37 are drawn to "the method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz to 1 MHz at an intensity that does not permanently damage the patient's skin" and "wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin".

Pearce et al, Mohr et al, Singer et al have been described previously.

Pearce et al, Mohr et al, Singer et al do not teach dependent claim limitations "the method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz to 1 MHz" and "wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin".

Mitragotri et al teach a method of applying ultrasound to promote delivering therapeutic doses of proteins across the skin of a patient (see the Abstract). Mitragotri et al teach that the ultrasound is used at a low frequency of about 20 kHz (see p. 852, 2nd col)(claim 25 and 37). Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins (page 850).

It would have been *prima facie* obvious at the time the invention was made to modify the method of reducing neurotransmitter release in a subdermal structure of a patient as taught by Pearce et al to include the transdermal patch of Mohr et al which incorporates drugs and skin enhancers (e.g. botulinum toxin and the enhancing agent) into the adhesive layer, non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum corenum as taught by Singer et al and a method of applying ultrasound to promote delivery of therapeutic doses of proteins across the skin of a patient as taught by Mitragotri et al because Mohr et al has demonstrated that this design of transdermal patch is simple but effective in delivering drugs to the skin, Singer et al teach that tape stripping enhances absorption of drugs into the skin and Mitragotri et al teach a method of applying ultrasound to promote delivery of therapeutic doses of proteins across the skin of a patient. It would be expected, absent evidence to the contrary, that a transdermal patch comprising botulinum toxin and an enhancing agent within the adhesive layer and using ultrasound to enhance delivery of the botulinum toxin to the skin would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of

a patient's skin that has been non-chemically disrupted by tape stripping, thereby reduce neurotransmitter release in a subdermal structure of the patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art that botulinum toxin inhibits or impairs neurotransmitters. See Pearce et al. Transdermal patches that incorporate drugs and skin enhancers into the adhesive layer are known in the art. See Mohr et al. Tape stripping is a non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum corenum. See Singer et al. It is well known in the art that ultrasound facilitates the delivery of drugs across the skin of a patient. See Mitragotri et al.

Thus, it would be obvious to reduce neurotransmitter release in a subdermal structure of a patient by using a transdermal patch that incorporates the drug or enhancing agent or into the adhesive layer and non-chemically disrupting the skin of the patient by tape stripping prior to applying the transdermal patch as well as applying ultrasound to facilitate the delivery of the botulinum toxin across the patient's skin because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that it is obvious to use a known technique to improve a known product that is ready for

improvement to yield predictable results. The combination of references teach the claimed invention absent convincing evidence to the contrary.

5. Claims 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearce et al, Mohr et al, Singer et al, Mitragotri et al as applied to claims 22-25, 28 and 36-37 above, and further in view of Yuzhakov et al *(U.S. Patent No. 6,565, 532 B1 published May 20, 2003)*.

Dependent claims 26-27 are drawn to "the method of 22 wherein the stratum corneum is disrupted by passing an electrical current from a first point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures".

Pearce et al, Mohr et al, Singer et al and Mitragotri et al have been described previously.

Pearce et al, Mohr et al, Singer et al and Mitragotri et al do not teach dependent claim limitations "wherein the stratum corneum is disrupted by passing an electrical current from a first point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures".

Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential

between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claims limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin (claim 26)" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures (claim 27)" are taught in the prior art reference. Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivered through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum toxin (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5).

It would have been *prima facie* obvious at the time the invention was made to use the electrodes as taught by Yuzhakov et al in the method of reducing neurotransmitter release in a subdermal structure of a patient because Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin providing a microneedle array structure comprising electrodes. It would be expected, absent evidence to the contrary, to modify the method or reducing

neurotransmitter release in a subdermal patient as taught by Pearce et al by using the microneedle array comprising electrodes that apply electric potential to a patient's skin as taught by Yuzhakov et al, the ultrasound applied to a patient's skin according to Mitragotri et al would enhance the delivery of the pharmaceutical compositions (e.g. botulinum toxin and an enhancing agent) incorporated within the adhesive layer of the transdermal patch (as taught by the combination of Mohr et al) into the subdermal layers of a patient's skin which has been non-chemically disrupted as taught by Singer et al.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art that botulinum toxin inhibits or impairs neurotransmitters. See Pearce et al. Transdermal patches that incorporate drugs and skin enhancers into the adhesive layer are known in the art. See Mohr et al. Tape stripping is a non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum corenum. See Singer et al. It is well known in the art that ultrasound facilitates the delivery of drugs across the skin of a patient. See Mitragotri et al. It is known in the art to move

charged drug molecules into the body by applying an electric current. See Yuzhakov et al.

Thus, it would be obvious to combine the transdermal patches which incorporates a drug and enhancing agent within the adhesive layer of a transdermal patch as taught by Mohr et al, wherein the skin of the patient has been non-chemically disrupted by the tape stripping method as taught by Singer et al using the technique of ultrasound as taught by Mitragotri et al to facilitate delivery of the drug through the skin and using the microneedle array to provide electrodes that apply electric potential to the patient's skin to further facilitate the delivery of a drug through a patient's skin as taught by Yuzhakov et al because KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007), disclosed that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results. The combination of references teach the claimed invention absent convincing evidence to the contrary.

***Status of Claims***

6. No claims allowed.

***Pertinent Art***

7. The prior art made of record and not relied upon is considered pertinent to Bauerova et al *(European Journal of Drug Metabolism and Pharmacokinetics, 2001, Vol. 1/2, pp. 85-94)* and Barry *(European Journal of Pharmaceutical Sciences 14, 2001, p. 101-114).*

## *Conclusion*

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Patent Examiner, Art Unit 1645
August 29, 2008